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Claim Amendments

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Claim 16 has been amended to define a method for regulating the tyrosine kinase signal transduction pathway in a human or other mammal with a compound of claim 1. Claims 17 and 22 have been amended to define methods for regulating the VEGF-induced signal transduction pathway in a human or other mammal with a compounds of claims 1 and 12, respectively. Support for these amendments is found on page 6, lines 8-11.

Rejection Under 35 USC§112, second paragraph

Claims 1-11 and 13-30 are not indefinite in using the term "metabolite" to define certain derivatives of the compounds of formula I . The compounds of formula I are clearly defined and therefore, the metabolities of these compounds are clearly defined. One skilled in the art would recognize that these derivatives are those produced by the metabolism of a compound of formula I. The specification indicates at page 21 that metabolites include oxidized derivatives of the compounds of formula I, with a particular example provided. Based on the applicants' disclosure and the state of knowledge of those skilled in the art, the term would not be considered indefinite. It is noted that a search of the claims in US patents for the terms "metabolite" or "metabolites" performed on the USPTO data base resulted in over 1300 hits. The common use of this term demonstrates that it is clear in meaning to those skilled in the art and considered acceptable under the statute.

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In providing the compounds of Formula I, applicants have identified components which are active as kinase inhibitors. The specification provides numerous ways to modify these compounds to form prodrugs which can be metabolized. For example, esters of appropriate compounds have been identified as suitable prodrugs on page 20, lines 16-20, and methods for synthesizing prodrugs are described in the 10 publications cited on pages 20-21 of the specification and incorporated by reference. To identify effective and preferred prodrugs is a matter of routine testing, performed by one skilled in the art on a day to day basis. No evidence has been presented to the contrary.

The enablement requirement, "is satisfied if, given what they [, those of ordinary skill in the art,] already know, the specification teaches those in the art enough that they can make and use the claimed invention without 'undue experimentation." See Amgen v Hoechst Marion Roussel, 314 F.2d 1313, 65 USPQ2d 1385 (Fed. Cir. 2003). The specification teaches those skilled in the art how to modify the compounds of formula I to form potential prodrugs. To identify effective or preferred prodrugs from applicants' disclosure would be routine for those of ordinary skill in the art, as demonstrated in the textbook by Wolff cited by the examiner. The textbook describes an example of a protocol to identify suitable prodrugs, which is no more than a routine test. To satisfy the statute, a "considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404.

Explicitly providing an example of a prodrug is not necessary to enable the claims. See, for example, In re Howarth, 654 F.2d 105, 210 U.S.P.Q. 689 (CCPA 1981) ("An inventor need not ... explain every detail since he is speaking to those skilled in the art."); In re Gay, 309 F.2d 769, 774, 135 U.S.P.Q 311 (CCPA 1962) ("Not every last detail is to be described, else patent specifications would turn into production specifications, which they were never intended to be.") There is no requirement that an applicant provide any working examples of the prodrugs claimed. The MPEP states that "compliance with the enablement requirement of 35 U.S.C.

112, first paragraph, does not turn on whether an example is disclosed." See MPEP § 2164.02.

No evidence has been presented which would demonstrate that the guidance provided by the specification is inadequate to enable the manufacture and use of the prodrugs of the compounds of Formula I such that the rejection based on these grounds should be withdrawn.

Similarly applicants traverse the rejection of claims 1-11 and 13-30 under 35 USC 112, first paragraph, based on the allegation that the specification does not provide an enabling disclosure for compounds where B is other than phenyl. The examiner alleges that the benzene ring of the working examples is non-basic while the pyridine ring and quinolinyl ring are strongly basic. No evidence has been presented to support this allegation or suggest such compounds would not have the claimed activity.

With respect to the alleged distinction between the compounds where B is not phenyl, the examiner's attention is drawn to co-pending application serial no. 09/640,780 (examples 24, 49, 161, 162, 163, 166, 198-199, 201-205, 208, 220, 222-227, 233, 236, 241, 259, 293, 344, 353, 354) and co-pending application serial no. 09/458,014 (examples 36, 39, 40, 168, 169, 171-179 and 182-184). The examples identified in these applications illustrate urea compounds where moiety "B" = pyridinyl that are effective inhibitors of raf and p38. In that analogous compounds with heterocyclic ring structures for moiety "B" have been shown to be effective kinase inhibitors, there is no basis to support the allegation that any compounds of formula I herein are ineffective and not enabled.

The specification provides sufficient guidance to those skilled in the art to make and use the compounds of formula I wherein B is not phenyl. To synthesize and test the activity of compounds where B is not phenyl would be routine. A considerable amount of routine experimentation is permissible in complying with the statute as discussed above. See Wands supra. In view of the state of the art as illustrated by the copending applications, it is not necessary to provide an example of a compound of formula I where "B" is not phenyl to enable the claims. As indicated above, there is no requirement that an applicant provide any working examples of

these compounds. See, for example, In re Angstadt, 537 F.2d at 502-03, 190 USPQ 214 (CCPA 1976) (deciding that applicants "are not required to disclose every species encompassed by their claims even in an unpredictable art"); Utter v Higara, 845 F.2d at 998-99, 6 USPQ2d 1714 (Fed. Cir. 1988) (holding that a specification may, within the meaning of Section 112, Para. 1, enable a broadly claimed invention without describing all species that claim encompasses).

The specification provides adequate guidance for one skilled in the art to make and use compounds of formula I wherein "B" is naphthyl, pyridyl, or quinolinyl such that there is no basis for the rejecting claims 1-11 and 13-30 under 35 USC § 112, first paragraph, for encompassing such compounds.

Applicants also traverse the rejection of claims 1-11 and 13-30 under 35 USC 112, first paragraph, based on the allegation that the specification does not provide an enabling disclosure for preventing or treating the disorders recited in the claims. Since claims 1-11 and 24-30 do not recite the treatment of disorders, applicants assume the basis for this rejection applies only to claims 14-23.

Claims 16 has been amended to define a method for regulating the tyrosine kinase signal transduction pathway using a compound of this invention. Similarly, claims 17 and 22 have been amended to define methods for regulating or the VEGF-induced signal transduction pathway with compounds of the present invention. These methods are clearly enabled in view of the activity, dosages and methods of administration disclosed in the application.. These claims do not recite the treatment of diseases such that the basis for the rejection is moot with respect to these claims.

The methods defined in claims 14, 15 and 23 are also clearly enabled in view of the disclosed activity, dosages and methods of administration. In addition, the publications cited on page 1 of the specification disclose the following:

1) Activation of the ras signal transduction pathway indicates a cascade of events that have a profound impact on cellular proliferation, differentiation, and transformation;
2) Raf kinase, a downstream effector of ras, is recognized as a key mediator of these signals;

3) The inhibition of the raf kinase signaling pathway has been shown to lead to the reversion of transformed cells to the normal growth phenotype;
4) The inhibition of raf kinase has been correlated in vitro and in vivo with the inhibition of the growth of a variety of human tumor types and
5) Small molecule inhibitors of raf kinase activity are important agents for the treatment of cancer.

No evidence has been presented to refute the findings or conclusions made in these publications. The activity of the compounds illustrated in the specification (raf inhibition) is associated with the treatment of hyper-proliferative disorders/cancer. No evidence has been presented that any compounds of this invention, as inhibitors of raf kinase, would not be effective in treating hyper-proliferative disorders/cancer. The specification provides ample guidance as to how to prepare pharmaceutical compositions with the compounds of this invention and how to administer these compositions in the treatment of cancers. The specification also provides dosage ranges for the various methods of administration. Given the extent of the disclosure provided, it would at most involve routine experimentation if any at all, for one of ordinary skill in the art to treat a hyper-proliferative disorder/cancer with a compound of this invention and therefore, claims 14, 15 and 23 are enabled.

Claims 18 and 19 are drawn to treating diseases characterized by abnormal angiogenesis or hyperpermeability and claims 20 and 21 are drawn to treating specific diseases related to or dependent on angiogenesis.

The Examiner has not presented any evidence or adequate reason for the rejection under 35 U.S.C. § 112, first paragraph of these claims. The courts have placed the burden upon the PTO to provide evidence shedding doubt on the disclosure that the invention can be made and used as stated; see, e.g., In re Marzocchi, 439 F.2d 220, 169 U.S.P.Q. 367 (CCPA 1971) (holding that how an enablement teaching is set forth, either by use of illustrative examples or by broad terminology, is of no importance.) The disclosure must be taken as in compliance with the enablement requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein. See In re Marzocchi, supra. No

such evidence or reason for doubting Applicants' disclosure has been provided. Only general statements and conclusions are made.

The examiner notes the state of the art would require screening of the compounds to determine whether the compounds exhibit the desired pharmacological activity for a specific disease. Such screening has not been shown to be "undue experimentation". As discussed in Wands, cited by the Examiner, a "considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." Such screening would simply be routine testing performed on a day-to-day basis by one skilled in the art.

In that no evidence has been presented to support the allegation that the claimed compounds would not be effective in treating any of the diseases set forth in claims 14, 15, 18-21 and 23, the rejection under 35 USC §112, first paragraph, should be withdrawn.

For the reasons discussed above, Applicants submit that all claims meet the requirements of 35 U.S.C. §112, first and second paragraphs and the rejections under this statute should be withdrawn.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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